A New Therapeutic Goal in MS: Maximizing Lifelong Brain Health
Its Scientific Basis and Role of Exercise

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THE LOSS OF BRAIN RESERVE EXPLAINS THE ONSET OF PROGRESSIVE DISABILITY IN MS AND UNIFIES RRMS, SPMS AND PPMS

Issues to be discussed:

- The relapsing remitting and progressive forms of MS are the same disease.
- Brain volume is related to brain/cognitive reserve capacity.
- The onset of progressive MS represents the loss of brain/cognitive reserve.
- Therefore, a comprehensive approach to the treatment of MS including effective use of DMTs, Exercise and Diet will be necessary to maximize lifelong brain health in persons with MS.
EVIDENCE RRMS, SPMS AND PPMS ARE THE SAME DISEASE:

Genetic, Epidemiological and Pathological Comparisons Between RRMS, SPMS and PPMS

- **No Genetic Differences**
  - Lundstrom W, et. al. No influence on disease progression of non-HLA susceptibility genes in MS. J Neuroimmunology 237 (2011) 98-100
  - International MS Genetics Consortium: Risk Alleles for MS Identified by a Genome wide study. NEJM 357 (2007) 851-862

- **No Familial Differences**
  - Ebers GC. Natural history of PPMS. Multiple Sclerosis 10 (2004) S8-S15

- **No Pathological Differences**
  - Lassmann H. Relapsing-remitting and primary progressive MS have the same cause(s)—the neuropathologist’s view:1. Multiple Sclerosis Journal 19(3) (2013) 266-267
  - Kuhlmann T. Relapsing-remitting and primary progressive MS have the same cause(s)—the neuropathologist’s view:2. Multiple Sclerosis Journal 19(3) (2013) 266-267

RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis

### Issues With Immunological Studies Comparing Relapsing and Progressive MS

![Bar Chart]

**Mean age data:**
- RRMS: Mean=36.5 years, SD=5.5 years
- SPMS: Mean=49.2 years, SD=5.5 years
- RRMS: Mean=38 years, SD=5.5 years
- PPMS: Mean=50.9 years, SD=5.5 years

N=14 studies
N=20 studies

The studies do not control for age and no findings are confirmed by a second study.

RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis
### Review of MRI Studies Comparing MS Subsets:

Table 1 Summary of imaging findings in different MS disease courses

<table>
<thead>
<tr>
<th>Brain</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gd enhancement*</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>T1</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Axonopathy*</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Whole brain</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Grey matter</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Magnetization transfer imaging</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Diffusion tensor imaging</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Proton magnetic resonance spectroscopy</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Cortical lesions* (frequency/extent*)</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Double-inversion recovery</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Spinal cord</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion load</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Axonphy*</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
</tbody>
</table>

*+, ++ and +++ indicate the relative extent of changes observed. For details please refer to the cited studies.

* Predicts progression of clinical disability

* Correlates with physical disability

### Comparison Of MRI Findings In MS Subtypes:

Table 2 MRI findings in subgroups of patients

<table>
<thead>
<tr>
<th>Brain MRI MS-like lesions</th>
<th>Clinically isolated syndrome (n=27)</th>
<th>Relapsing-remitting MS (n=66)</th>
<th>Secondary-progressive MS (n=19)</th>
<th>Primary-progressive MS (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/23 (80)</td>
<td>6/65 (100)</td>
<td>17/19 (89)</td>
<td>18/18 (100)</td>
<td></td>
</tr>
<tr>
<td>Normal MRI</td>
<td>5/25 (20)</td>
<td>9/65</td>
<td>2/19 (11)</td>
<td>0/18</td>
</tr>
<tr>
<td>1-2 lesions</td>
<td>4/25 (16)</td>
<td>2/65 (3)</td>
<td>2/19 (11)</td>
<td>2/18 (11)</td>
</tr>
<tr>
<td>&gt;3 (no Barkhof criteria)</td>
<td>2/25 (8)</td>
<td>6/65 (9)</td>
<td>1/19 (5)</td>
<td>2/18 (11)</td>
</tr>
<tr>
<td>Fulfilled modified Barkhof criteria</td>
<td>14/25 (56)</td>
<td>5/65 (88)</td>
<td>14/19 (74)</td>
<td>14/18 (78)</td>
</tr>
<tr>
<td>Gd enhancement</td>
<td>8/18 (44)</td>
<td>2/190 (53)</td>
<td>3/15 (28)</td>
<td>4/49 (44)</td>
</tr>
<tr>
<td>Spinal cord MRI</td>
<td>8/11 (73)</td>
<td>9/12 (75)</td>
<td>3/4 (75)</td>
<td>7/9 (78)</td>
</tr>
</tbody>
</table>

Percentages are shown in brackets.

SO WHY DO PROGRESSIVE MS PATIENTS HAVE APPARENTLY LITTLE RESPONSE TO DMTS?

Important Observations Relevant to Understanding Response to DMTs in RRMS, SPMS and PPMS

- Relapse rates decrease as a function of age and may stop in many patients in the 6th or 7th decade of life.
- Relapses reflect only a small part of the Gd-enhancing inflammatory disease seen on MRI, which also decreases as a function of age.
- Probability of onset of progressive MS is most strongly related to age and magnitude of brain atrophy.
- Brain atrophy reflects neurodegeneration and starts at the onset of MS—MS is a grey matter disease too.
- Most disease activity in RRMS patients is subclinical and is masked by cortical remodeling/plasticity and other compensatory mechanisms—So, what happens when they run out of the capacity to compensate (brain reserve)???

RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; Gd, gadolinium
Relapses in MS are Age and Time-dependent

From the population perspective, the impact of any therapeutic agent targeting the inflammatory processes in MS, and hence ability to modify recurrence of relapses, has the greatest potential during periods of high disease activity


Inflammatory Cortical Disease in Early MS Leads to Neuronal Death

Neuronal injury evidenced by presence of pyknotic neurons

Microglia close to neurons

T cells close to oligodendrocytes

Cortical demyelinating lesions are frequent, inflammatory, and strongly associated with meningeal inflammation in patients with early MS

Cortical Atrophy is Detected in Clinically Isolated Syndrome

Normalized Cortical Volume (mL)

- P<0.0001 for NC vs. CIS
- P<0.0001 for NC vs. RRMS

Values:
- NC: n=28, 540 mL
- CIS: n=18, 550 mL
- RRMS: n=351, 560 mL


NC, normal controls; CIS, clinically isolated syndrome; RRMS, relapsing-remitting multiple sclerosis.

Value of Brain Atrophy as an Outcome Measure in MS

- Brain atrophy provides additional information on aspects of MS disease/pathological features
  1. Brain atrophy proceeds faster in MS patients vs. healthy controls
  2. Healthy controls: 0.1–0.4% per year
  3. Early stage MS: 0.7% per year
  4. RRMS: 0.5–1.35% per year
  5. Brain atrophy occurs early, progresses throughout the course of MS
  6. Brain atrophy reported as best MRI predictor for future disability and is a correlate to brain reserve capacity

An 8-year Follow-up Study: Brain Atrophy Predicted Probability of Reaching EDSS of 6¹

- Patients (n = 138) were categorized into quartiles based on the amount of atrophy during the phase 3 trial (i.e. change in brain parenchymal fraction [BPF] from baseline to year 2)
- 44 patients reached EDSS ≥ 6.0 by year 8

Early Neuronal Injury Is Masked By Compensation And Reorganization¹,²

Healthy Control  
CIS Patient

Clinical exam reveals fully normal functioning of right hand during simple motor task in CIS patient

fMRI reveals functional cortical changes

Ongoing damage may go unrecognized until it is too late

Brain and Cognitive Reserve


BCR, brain cognitive reserve

Molecular mediators
- Epigenetics (e.g. DNA methylation, histone modifications)
- Activity-dependent gene expression (e.g. neurotrophins)
- Protein processing and trafficking
- Signalling pathways

Cellular mediators
- Neurogenesis
- synaptic plasticity
- Gliogenesis
- Angiogenesis

Systems effects
- Network plasticity and functional compensation
- Efficiency of information processing and storage
- Connectivity and functional redundancy

Cognitive Reserve:

1. Stern Y. Neuropsychologia. 2009

Point of inflection

Incident dementia

Person with high reserve
Person with low reserve

Alzheimer's disease neuropathology
Brain/Cognitive Reserve Protects Against Cognitive Disability in MS¹

Brain reserve protects against disease-related cognitive decline

Cognitive reserve independently protects against disease-related cognitive decline over and above brain reserve


Cross-sectional Comparison of Cognitive Reserve Groups by Symptom Inventory Subscale Means

Findings suggest higher active and passive reserve scores are associated with better generic and disease-specific outcomes

Loss of Brain/Cognitive Reserve Explains Onset of Progressive MS

Loss of Brain/Cognitive Reserve and onset of progressive disability

Stages of MS:

- Relapsing MS → Transitional MS → Progressive MS

What is the cause of progression of disability in SPMS and PPMS?

- Ongoing inflammatory disease activity in active MS.

- Loss of function due to disuse. (musculoskeletal and neurologic)

- Age related loss of function. (musculoskeletal and neurologic)
The Window of Therapeutic Opportunity in MS: Evidence from Alemtuzumab Trial

The window of opportunity: evidence from the alemtuzumab trial

1. Coles A, et al. J Neurol 2006; Comparison of change in disability between the relapsing–remitting and secondary progressive cohorts. The data are annualized to allow comparison between time epochs of different duration. * p < 0.05; ** p < 0.01; *** p < 0.001 (Mann–Whitney U test)
RATIONALE FOR COMPREHENSIVE APPROACH TO THE MANAGEMENT OF MS:

Effect of Co-Morbidities on Disability in MS:

Table 3: Odds ratios and 95% CIs for the association of comorbidity category at diagnosis and degree of disability at diagnosis in white NARCOMS participants enrolled within 2 years of diagnosis (n = 2,237)

<table>
<thead>
<tr>
<th>Comorbidity category</th>
<th>OR</th>
<th>95% CI</th>
<th>OR</th>
<th>95% CI</th>
<th>OR</th>
<th>95% CI</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Moderate vs mild</td>
<td></td>
<td>Severe vs mild</td>
<td></td>
<td>Moderate vs mild</td>
<td></td>
<td>Severe vs mild</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td>1.51</td>
<td>1.12-2.05</td>
<td>1.06</td>
<td>0.77-1.44</td>
<td>1.32</td>
<td>0.97-1.80</td>
<td>0.87</td>
<td>0.63-1.20</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>1.54</td>
<td>1.04-2.28</td>
<td>1.81</td>
<td>1.25-2.63</td>
<td>1.35</td>
<td>0.91-2.01</td>
<td>1.55</td>
<td>1.06-2.27</td>
</tr>
<tr>
<td>Mental</td>
<td>1.29</td>
<td>0.97-1.71</td>
<td>1.62</td>
<td>1.23-2.14</td>
<td>1.23</td>
<td>0.92-1.63</td>
<td>1.53</td>
<td>1.16-2.02</td>
</tr>
<tr>
<td>Overweight</td>
<td>1.08</td>
<td>0.78-1.50</td>
<td>1.03</td>
<td>0.74-1.42</td>
<td>1.02</td>
<td>0.74-1.43</td>
<td>0.93</td>
<td>0.68-1.29</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.38</td>
<td>1.02-1.87</td>
<td>1.24</td>
<td>0.91-1.67</td>
<td>1.33</td>
<td>0.98-1.80</td>
<td>1.16</td>
<td>0.86-1.57</td>
</tr>
</tbody>
</table>
Effect of Diet Related Diseases on Disability in MS:

Benefits of Exercise in MS:
- Improved Aerobic Capacity
- Improved Strength
- Improved Endurance
- Improved Balance
- Improved Fatigue
- Improved Bowel/Bladder Function
- Improved Quality of Life
- Improved Self Efficacy
- Improved Depression
CONCLUSION:

The key therapeutic goals in MS are to preserve brain volume in early disease, enhance brain reserve and maximize lifelong brain health.